

## METASTATIC INOCULATION OF A MENINGIOMA BY CANCER CELLS FROM A BRONCHIOGENIC CARCINOMA \*

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Experimental and clinical investigations on cancer for the last two decades seem to favor the conception that the development of an epithelial malignant disease is largely influenced by immunobiological factors. Apparently not only does the host itself offer resistance to the development of a cancer (natural immunity) but resistance toward the implantation of cancer can be induced experimentally in animals (active immunity). Thus Ehrlich <sup>1</sup> showed that rats with healed mouse cancer are immune to a reinfection, and also that mice with actively growing tumors are mostly immune to secondary implants. Similarly Murray <sup>2</sup> reported that mice with a tar cancer resist a "superinfection" with a second tar cancer, and that a tar tumor will not "take" in a mouse following the extirpation of a previously existing spontaneous tumor. If these observations are correct and also if one is permitted to draw analogies between man and animal, a person with cancer ought to resist the development of a new tumor.<sup>3</sup>

The problem of benign tumors is different in that the condition represents obviously a purely local disease, and for this reason the coexistence in the same person of multiple benign tumors or of a malignant and a benign neoplasm is merely one of casual interest only.

Whether a preëxisting benign tumor provides a suitable soil for the growth of malignant tumor cells and how the latter will behave under the circumstances has been investigated experimentally by Ehrlich as will be told; but it is especially unusual to have the opportunity to study this symbiosis in man.

In the case to be discussed the patient had multiple primary tumors — a leiomyoma of the uterus, and a meningioma in which carcinoma cells were found to be growing.

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## REPORT OF CASE

*Clinical History:* A white woman, aged 57, entered the Peter Bent Brigham Hospital March 14, 1923 with the complaint of pain in the lumbar region extending down the left leg to the knee, inability to walk and weakness of the right hand. The left breast had been removed twenty-five years ago at the St. Luke's Hospital, New York City, for an unknown cause, and she has been well since that time.

The present illness began with a dull, persistent, bilateral lumbar pain five months before admission. Two weeks later the pain extended down the left anterior thigh and left gluteal region. There also was trouble in walking, night sweats from eight to twelve weeks, and hemoptysis for two weeks, a spoonful in amount.

On physical examination the abdomen was rigid and the left lower abdominal quadrant was definitely tender. Several small nodules were palpated on the left side of the cervix uteri.

The blood pressure was systolic 110, diastolic 60. The blood and urine were normal. The spinal fluid showed no pathological changes.

*March 24, 1923.* Roentgen-ray examination of the chest disclosed an area of consolidation in the left base. The thorax was slightly asymmetrical, the left side being less expanded than the right. The left diaphragm was higher than the right.

*March 31, 1923.* The patient was operated upon for a myoma of the uterus. The wound healed slowly owing to a mild infection. The patient coughed up blood.

*May 22, 1923.* A re-examination of the chest showed a diffuse mottling which resembled miliary tuberculosis throughout both lungs. The left lower base was hazy.

*May 31, 1923.* The patient died.

## AUTOPSY REPORT

*Anatomical Diagnoses:* *Left bronchiogenic carcinoma with metastases to bronchial lymph nodes, liver, adrenals, bone and brain. Meningioma, infiltrated by cancer. Leiomyoma of uterus. Absence of left breast removed twenty-five years previously. Acute aortic endocarditis. Infarction of spleen and kidneys, and septicemia.*

The body was found to be well developed and well nourished. There was an edema of the ankles and legs.

The pleura on the left side was adherent to the thoracic wall. Numerous tumor nodules could be seen in the intercostal muscles and below the periosteum of the ribs.

The heart showed warty, recent vegetations at the aortic valve.

The left lung weighed 580 gm., the right lung 520 gm. The left lung contained a large tumor mass in the lower lobe and in the posterior axillary line just below the interlobar fissure. The two lobes

were adherent by tumor. In this area the lung was contracted, owing to a newgrowth which caused a puckering of the pleura. On section the tumor mass which was 6 cm. in diameter radiated into the lung in various directions. On dissecting down the bronchus it was found that near the tumor the bronchus was definitely roughened and the newgrowth seemed to be present in its wall. Along the course of the bronchi and peribronchial lymphatics numerous tumor nodules could be seen radiating to the root of the lung where very large lymph nodes were found, the largest of which measured 5 cm. in diameter. This extended down the posterior mediastinum to the diaphragm. The nodes at the hilum of the right lung were quite normal. The right lung was literally speckled with small, white, creamy nodules which varied in size from 1 mm. to 0.5 cm. in diameter.

The liver weighed 1,335 gm. and was normally plastic and friable. However, it contained numerous tumor nodules measuring from 2 mm. to 4 cm. in diameter.

Both suprarenals were enlarged and on section thin suprarenal cortex could be seen surrounding grayish tumor masses.

The first lumbar vertebrae were compressed to 1.5 cm. in width and also apparently contained tumor.

*Brain:* The brain weighed 1,300 gm. In the left posterior parietal region was a metastatic nodule which arose at the site of the longitudinal sinus. It measured 1.5 cm. in length and seemed to extend into the secondary sinuses. It was definitely adherent to the dura by clot, and its base seemed in places to have infiltrated the dura. When the skull cap was held to the light it showed areas of increased density more marked than one ordinarily sees in a normal skull, and perhaps evidence of infiltration with tumor.

*Meningioma:* When the calvarium was removed an elevated tumor mass 2 cm. in diameter was found over the right frontal lobe. It was invested by the meninges, being moderately soft and pinkish gray. In gross the appearance of this tumor was that of a meningioma (dural endothelioma).

#### MICROSCOPIC FINDINGS

*Lungs:* The tumor is made up of a columnar epithelium with an oval, vesicular nucleus and a deeply stained nucleolus. The cells have an adenomatous arrangement and are supported by a fine

stroma. In sections taken from the bronchi the tumor shows invasion of all the coats. The circular muscle layer is markedly thickened. The seromucous glands, however, are intact being surrounded by a thick wall of small, round cells. The tumor invades largely the capillaries and veins.

In the suprarenals the tumor closely resembles that of the lungs, while in the liver the stroma is rather abundant, dense and fibrous.

In the brain the tumor is found as small nodules composed of cells identical by their shape and arrangement with those of the pulmonary newgrowth.

*Meningioma:* A cross-section of the entire tumor is studied. In areas where the growth is not invaded by cancer it shows the customary histology characteristic of this neoplastic group. There are numerous psammoma bodies. In places invaded by the malignant epithelial cells (Figs. A and B) the cells of the meningeal newgrowth are dissociated, forming a coarse network. The malignant tumor here is insinuated between the meningioma cells, and the individual cells have adhered to the cellular fibers of the meningioma forming bud-like elevations. Cancerous invasion is more conspicuous at the periphery of the meningioma, however the thick fibrous capsule is not invaded by the malignant neoplasm. In areas where the cancer predominates the meningeal tumor shows a good deal of necrosis.

#### COMMENT

The early occurrence of widespread metastases in bronchiogenic cancers has been discussed by the present writer elsewhere.<sup>4</sup> The significance of this report lies in the fact that the malignant epithelial tumor diffusely infiltrated the meningioma.

Following the successful experiments with the induction of cancer in laboratory animals, Ehrlich conceived the idea of studying the pathogenesis of the so-called mixed tumors in human beings. For that purpose he<sup>5</sup> and Apolant<sup>6</sup> inoculated animals with mixtures of two or three tumors from different germinal layers, like sarcoma and carcinoma, or chondroma and sarcoma.

When a mixture of a carcinoma and sarcoma was inoculated into animals this led to a tumor known as a *carcinoma sarcomatodes* in which the parenchyma was made up of the malignant epithelial cells, while the stroma was sarcomatous. There occurred then an

amalgamation of the two different neoplastic types which resulted in the formation of a new type of tumor.

By injecting into an animal a carcinoma or a sarcoma with a chondroma no amalgamation occurred and both tumors grew side by side keeping their own properties. By mixing, for instance, a chondroma with a sarcoma it was noticed that the benign tumor contained isolated necrotic areas surrounded by actively growing sarcoma. In some areas the tumors were entirely separated so as to represent two distinct neoplasms.

Heiman<sup>7</sup> in a recent study utilized Ehrlich's procedure to bring forward the claimed ineffectiveness of epithelial malignant tumors. He inoculated rapidly growing carcinomas and sarcomas of the rat in the center of large spontaneous or transplanted fibromas of the breast of other rats. This resulted in the growth of a malignant tumor with, however, a greatly reduced proliferative activity of the carcinoma. The epithelial malignant tumor continued to remain encysted in the center of the benign tumor while sarcomas grew along the track of the needle infiltrating the fibrous tissue and ultimately escaped into the tissue of the host. The benign newgrowth (according to Heiman) seemed to play an entirely neutral rôle even though highly malignant cells were present in the center. This, then, according to the same author, is further evidence against an organism being responsible for the growth of malignant tumors, for it might be expected that if such an organism were present it would stimulate the benign tumor to become malignant.

It will be seen that the clinical case herein reported imitated very closely the experiments of Ehrlich, of Apolant, and of Heiman. The bronchiogenic carcinoma invaded the meningeal newgrowth without being amalgamated with it, and retained therefore its individual characteristics. It grew actively, squeezing out the "host." The carcinomatous cells had split the solid rows of the meningioma giving the impression that they were utilizing its cellular fibrillae as a means of advance.

A few workers are still uncertain whether malignant conditions induced in animals are akin to those seen in human beings. Ribbert (quoted by Lewin<sup>8</sup>) was of the opinion that experimental and human cancer are probably different diseases and that in the problem of epithelial malignant disease no analogies should be drawn between these two species. This of course was denied in many instances.

The case here described demonstrates once more that even "bizarre" neoplastic conditions induced in laboratory animals by Ehrlich and others are often an exact counterpart of what one sees in conditions encountered in the clinic.

#### REFERENCES

1. Ehrlich, P. Experimentelle Karzinomstudien an Mäusen. Jena, 1908.
2. Murray, J. A. Twenty-sixth Scientific Report. The Imperial Cancer Research Fund, London, 1927-1928.
3. Fried, B. M. Primary double cancer. *Arch. Path.*, 1928, **5**, 565.
4. Fried, B. M. Primary carcinoma of the lungs. *Arch. Int. Med.*, 1925, **35**, 1.  
Further study with particular attention to incidence, diagnosis and metastases to the central nervous system. *Arch. Int. Med.*, 1927, **40**, 340.
5. Ehrlich, P. Experimentelle Studien an Mäusetumoren. *Ztschr. f. Krebsforsch.*, 1907, **5**, 59.
6. Apolant, H. Ueber künstliche Tumormischungen. *Ztschr. f. Krebsforsch.*, 1908, **6**, 251.
7. Heiman, J. Implantation of rat carcinoma and sarcoma with benign fibroadenoma. *J. Cancer Research*, 1928, **12**, 73.
8. Lewin, Carl. Die Aetiologie der bösartigen Geschwülste. Julius Springer, Berlin, 1928.

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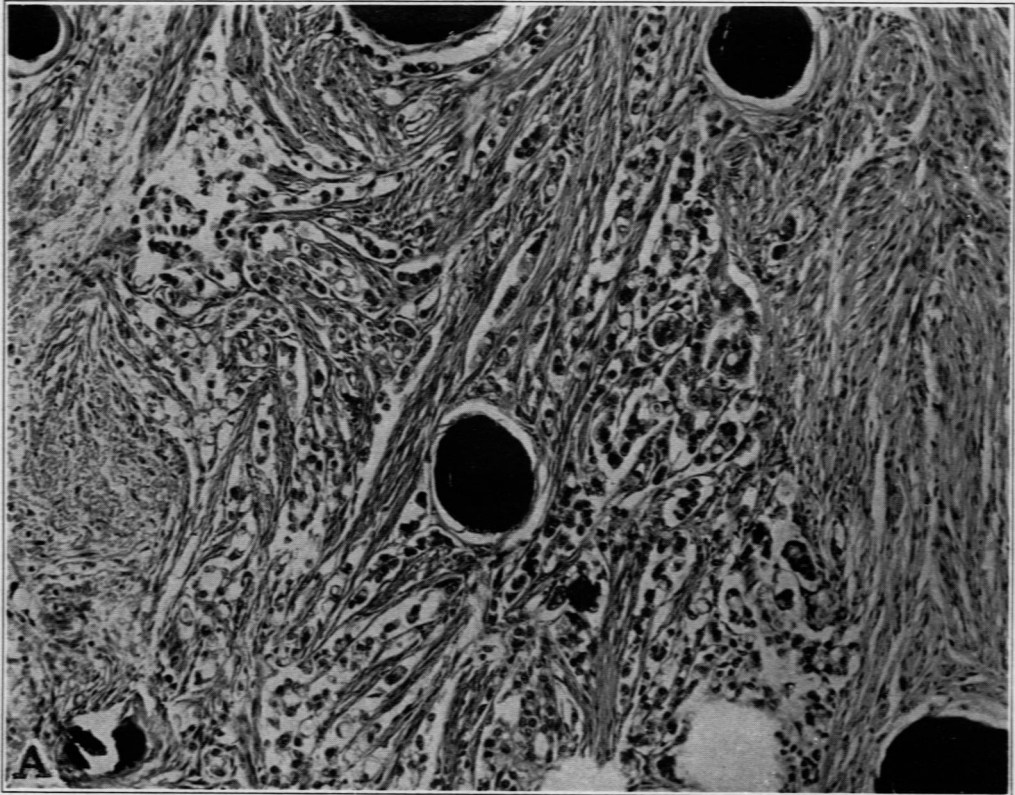
#### DESCRIPTION OF PLATE

##### PLATE 16

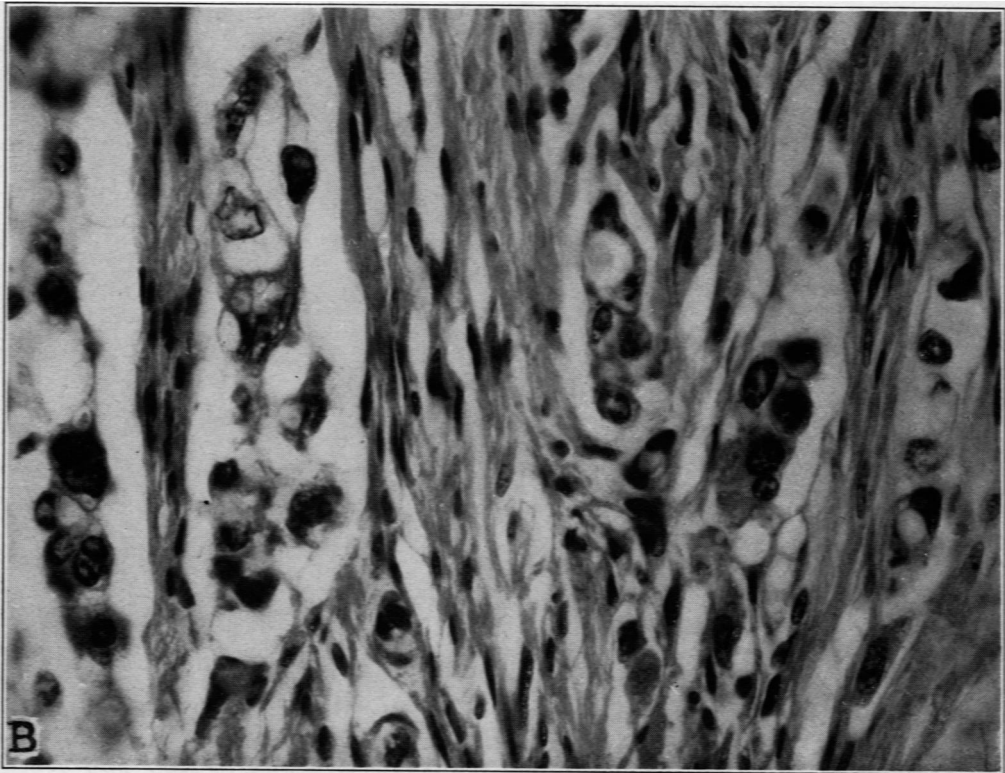
Showing invasion of the meningioma by the cells of a cancer which had originated in the bronchus. Hematoxylin and eosin.

Fig. A  $\times 150$ .

Fig. B  $\times 635$ .



A



B

Fried

Inoculation of Meningioma by Cancer Cells